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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,081	10/24/2001	Avi J. Ashkenazi	GNE.2630P1C69	4135

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EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,081	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-65,68-70 and 74-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-65,68-70 and 74-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/16/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Amendment dated 9/16/05 has been entered into the record.

B. Claims 58-65, 68-70, and 74-87 are pending and are the subject of this Office Action.

C. The Information Disclosure Statement, filed 9/16/05, has been entered into the record.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Specification

A. All objections to the specification have been withdrawn in view of Applicants' amendments to the specification and title.

3. Claim Objections

A. The objection to claims 58-65, 68-70, and 74-77 has been withdrawn in view of Applicants' amendment to the claims to remove "as shown in."

4. Claim Rejections - 35 USC § 101

A. No rejection of claims 58-65, 68-70, and 74-77 under 35 USC 101 has been made in the instant application since utility was provided by the rod photoreceptor assay. The Examiner in inadvertently stated that utility was provided by the endothelial cell apoptosis assay. Regardless of the lack of a utility rejection, Applicants argue the utility for all of the recited assays. Their arguments will be addressed in both this section and under 35 USC 112, first paragraph, below.

Applicants argue that the Retinal Neuronal Survival Assay (Assay #52) has utility. They discuss the assay used and state that the neural retina was isolated. Applicants compare their assay to that of Otori et al. Applicants argue that Otori measured the effects of compounds on RGCs and, as with the present invention, determined viability using AM staining. The Examiner has concluded that AM staining is a non cell-specific means to measure cell viability. This appears not to be an issue in the present situation since, according to Applicants, they have a culture of retinal neuron cells. The Examiner interprets the term "retinal neuronal cell population" as a population of a single-type of cells. In other words, the ordinarily skilled artisan would recognize that all "retinal neuronal cells" are anatomically and physiologically the same type of cell with identical structural and functional properties. If this is not the

case the issue would be one of the use of general AM staining to identify cell survival. If the population of "neuronal cells" is, in fact, a mixed population, then it would be unclear how the use of AM staining would be able to identify a specific population of cells affected by the polypeptides, antibodies, etc. of the present invention. This would be important since the utility of any compound, such as the one of the present invention, for increasing cell survival would only be granted in Applicants, in fact, knew for which specific cell type survival was increased. A compound which generally increases a mixture of cell types would not have utility in the present application since Applicants have not identified a specific disease state to which the polypeptides or antibodies of the present invention can be effective in treating. **For clarification of the record, however, Applicants are urged to address the Examiner's conclusion that, in fact, "retinal neuronal cells" are one population/type** of cell. Furthermore, Otori teach that glutamate has been implicated in death of RGC characteristics of glaucoma. RGCs, as opposed to retinal neuronal cells, are a mixed population of cells. The fact that Otori demonstrated the effects of glutamate on this mixed population does necessarily correlate to, or provide utility for, compounds which affect retinal neuronal cells. These are different populations of cells. Furthermore, no correlation to any disease state has been provided for the polypeptides (i.e. the retinal neuronal cells) of the present invention. It would not be expected, in absence of evidence to the contrary, that glaucoma, which may have some characteristics associated with RGCs, would necessarily have characteristics influenced by, or treatable by affecting retinal neuronal cells. Finally, Applicants state on page 23 of their Response dated 9/16/05 that anything above a 30% increase in survival was considered positive. However, Applicants have not provided an associated utility with this number. It is not clear if a survival rate of 30% above control would effectively treat any disease, especially in the absence of any disclosed diseases associated with retinal neuronal cells, or which can be treated with the polypeptides and antibodies of the present invention.

Applicants further argue on pages 24-25 of their Response dated 9/16/05 that promoting apoptosis in endothelial cells has utility in inhibiting tumor progression and cite Benjamin et al. as a model for the role of endothelial cell apoptosis in tumor progression. The question is whether the assay of Benjamin can be used to provide utility to the assay of the present invention (Assay 109). Applicants argue that Benjamin teach that limiting angiogenesis would retard tumor growth. Therefore, Applicants conclude that, since their PRO induces apoptosis in endothelial (HUVEC), it can be used to treat tumor progression. These arguments have been considered, but are not deemed persuasive. First, Applicants have not shown that their assay is identical to that of Benjamin et al. Applicants have, respectfully, not demonstrated that the PRO of the present invention is selective to HUVEC. No controls using cells other

than HUVEC cells have been implemented. The PRO of the present invention may be a non-selective killer of a wide variety of cells, other than HUVEC. Benjamin teach that VEGF is involved in endothelial cell apoptosis. Therefore, it appears that all that can be concluded from the Benjamin assay is that mediators or VEGF may have utility in tumor progression. However, the PRO of the present invention has not been shown to modulate VEGF. A similar question arises for the studies of Jiang et al. (cited by Applicants). It is not clear if apoptosis was actually induced in the HUVEC of the invention, or if the PRO of the invention simply killed the cell by other means (e.g. a general, non-selective toxin). Applicants have not demonstrated that an ELISA would detect apoptotic cells vs. cells killed by other mechanisms. Furthermore, the specification (p 356) states that samples with levels > 130% were considered positive for induction of apoptosis." However, Applicants have not taught whether this number correlates to a level effective to induce apoptosis in a "real world" scenario. No in vivo data has been provided in the specification. Though in vivo data is not necessarily required in an application, it may still be important when attempting to demonstrate a "real world" utility for in vivo situations as opposed to basing a finding of utility simply on in vitro data which does not necessarily correlate to in vivo use. It is not known how one would be able to specifically target the endothelial cells which make up the tumor "microenvironment."

5. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. Claims 58-65, 68-70, and 74-77 remain rejected and new claims 78-87 are also rejected under 35 USC 112 for the reasons already of record on page 3-4 of the Office Action dated 6/17/05 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

Applicants argue that Fontaine et al. and Streichert et al. describe essentially the same assay as Example 111 of the present invention. Therefore, these references support Applicants' assay and, therefore, enablement. These arguments have been considered, but are not deemed persuasive. Two questions are raised in reading Applicants' arguments. First, Applicants refer on more than one occasion to the fact that the assays of the present invention are "*essentially the same*" as those of Fontaine and Streichert. However, Applicants have not taught how the assay of the present invention differs from the prior art. It is not known what essential steps or elements are different between the present invention and

cited art. Applicants are urged to explain the distinctions, even if the response is accompanied by arguments as to how the differences are not important to the outcome of the present invention. Another issue raised by Applicants' arguments, and in reading Steichert, is that Streichert recite using retinas which were "isolated" from the pigmented epithelium whereas the present invention discloses that the neural retina is "dissected away" from the pigment epithelium. This leaves the question as to whether the neural retinal cells still were "contaminated" with pigment epithelium or other cells. Clarification is requested. Therefore, though Applicants' statement regard Fontaine "that agents which promote survival of photoreceptors are useful in therapeutic approaches to eye disorders without needing to promote growth of new neurons" may be true, for the above reasons, the present invention is not enabled.

Applicants further argue that Example 110 of the instant specification is also enabled, for reasons including that it is similar to those of both Otori and Levin. Again, Applicants have stated that the assays are "similar" without explaining the differences between the present assay and those of the prior art. The claims are also not enabled for the reasons given in the above rejection under 35 USC 101. In addition, Applicants' arguments regarding the HUVEC assay are also not enabled for the reasons provided in the above rejection under 35 USC 101.

Applicants further argue that "the specification provides the amino acid sequence of the polypeptide of SEQ ID NO:216, with or without the signal peptide, as well as the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209847. Thus the subject matter of Claims 63-65 is clearly enabled by the specification." This argument has been considered, but is not deemed persuasive for the reasons stated above and in the rejection under 35 USC 101. Again, Applicants have only demonstrated that the assays of the present invention in which the PRO tested positive were "similar" to those in the art.

In addition, Applicants argue that pages 180-183 of the specification teach what changes can be made to the full-length protein of SEQ ID NO:216 to retain function (i.e. methods of determining percent identity) and that the artisan can easily "make and test" variants. However, the specification only provides a general teaching of how to go about changing residues in the protein and how to look for changes in protein function. There are no specific teachings of which specific amino acid residues to alter and which to maintain in order to maintain the desired function of the full-length protein. Respectfully, the bar for enablement is "make and use" not "make and test."

It is believed that all pertinent arguments have been addressed.

6. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 58-65, 68-70, and 74-77 remain rejected and new claims 78-87 are also rejected under 35 USC 112 for the reasons already of record on page 2-5 of the Office Action dated 6/17/05 as well as for the reasons given in the above rejection under 35 USC 101. The rejection of claims 63-65 and 68 has been withdrawn in view of the fact that the full-length proteins of, or DNA encoding, SEQ ID NO:216 is adequately described in the specification. Applicants' arguments regarding % identity have been fully considered, but are not found to be persuasive. Regardless, respectfully, of the fact that all of the claims recite a specific function, Applicants have not adequately described which amino acid residues can be altered in order to retain the functional characteristics of the full-length protein of SEQ ID NO:216. While it may be physically possible for the artisan to test each variant of SEQ ID NO:216, the possible number of variants is astonishing and will fall easily in the millions. SEQ ID NO:216, alone, is clearly insufficient to describe the claimed genus of protein variants. In addition, Applicants argue that pages 180-183 of the specification teach what changes can be made to the full-length protein of SEQ ID NO:216 to retain function (i.e. methods of determining percent identity) and that the artisan can easily "make and test" variants. However, the specification only provides a general teaching of how to go about changing residues in the protein and how to look for changes in protein function. There are no specific teachings of which specific amino acid residues to alter and which to maintain in order to maintain the desired function of the full-length protein.

It is believed that all pertinent arguments have been addressed.

7. Claim Rejections - 35 USC § 112, second paragraph

A. All rejections under 35 USC 112, second paragraph, have been withdrawn in view of Applicants' amendments to, or cancellation of, the claims.

7. Claim Rejections - 35 USC § 102

A. The rejection of claims 71-73 under 35 USC 102 has been withdrawn in view of Applicants' cancellation of the claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on T-F 10 AM – 7 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert Landsman/
Robert Landsman
Primary Examiner
Art Unit 1647